Saudi Journal of Medicine and Public Health

https://saudijmph.com/index.php/pub

https://doi.org/10.64483/202412553

Quantitative Imaging Biomarkers for Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling in Clinical Trials: A Review of Methodologies and Applications

Hamad Abdulelah H Alkhayyal [(1)] , AMAL Ibrahim Samah Alruwaili [(2)] , Mohammed Mousa Muyidi [(3)] , Mousa Mohammed Ali Bahkali [(4)] , Raef Abdu Ahmad Kamli [(5)] , Sami Musaad Alotaibi [(6)] , Maher Omran Ali Alotaibi [(6)] , Dalal Ali Saleh Almadeh [(6)] , Talal Mubarak Shuraim Al-Mughairi [(7)] , Ibrahim Mohamed Hamed Somaily [(8)] , Amani Ayeed Madee Alshahrani [(9)] , Meshal Muflih Almutairi [(10)] , Maryam Mohammed harthi [(11)]

(1) King Salman Hospital, Ministry of Health, Saudi Arabia,
(2) Sakaka – Al Jouf Region,Maternity and Children's Hospital, Ministry of Health, Saudi Arabia,
(3) Abu Arish General Hospital, Ministry of Health, Saudi Arabia,
(4) Jazan Health Affairs, Saudi Ministry of Health, Saudi Arabia,
(5) King Fahad Central Hospital, Jazan, Ministry of Health, Saudi Arabia,
(6) Afif Hospital, Ministry of Health, Saudi Arabia,
(7) Afif General Hospital, Ministry of Health, Saudi Arabia,
(8) Altwal General Hospital, Ministry of Health, Saudi Arabia,
(9) King Abdullah Hospital, Bisha, Ministry of Health, Saudi Arabia,
(10) Al-Mithnab General Hospital, Ministry of Health, Saudi Arabia,
(11) Imam Abdulrahman Al-Faisal Hospital, Ministry of Health, Saudi Arabia

Abstract

Background: The high cost and failure rate of late-stage oncology and neurology drug trials underscore the critical need for robust early-phase decision-making tools. Traditional pharmacokinetic/pharmacodynamic (PK/PD) modeling, which relates drug exposure to a biological effect, often relies on plasma drug levels and sparse tissue biopsies, providing an incomplete picture of in vivo drug behavior and heterogeneity. Concurrently, advancements in medical imaging have moved beyond qualitative assessment to provide repeatable, non-invasive, and spatially resolved quantitative data on tumor morphology, cellularity, perfusion, and metabolism.

Aim: This narrative review aims to analyze the convergence of these two fields by examining how quantitative imaging biomarkers (QIBs) are integrated into PK/PD modeling frameworks within clinical trials.

Methods: A comprehensive literature search was conducted across PubMed, Scopus, and Web of Science for English-language articles (2010-2024).

Results: QIBs from modalities like Dynamic Contrast-Enhanced MRI (DCE-MRI), Diffusion-Weighted Imaging (DWI), and Positron Emission Tomography (PET) provide critical parameters (e.g., K*trans*, ADC, SUV) that can populate computational PK/PD models. These imaging-informed models enable the non-invasive estimation of drug delivery to tissues, receptor occupancy, and the time-course of pharmacologic effect, offering a powerful tool for dose selection, go/no-go decisions, and patient stratification in early-phase trials. However, significant challenges in standardization, validation, and regulatory acceptance persist.

Conclusion: The integration of QIBs into PK/PD modeling represents a transformative paradigm in translational drug development. It bridges molecular pharmacology and in vivo imaging, enabling a more holistic, mechanistic understanding of drug action. For this potential to be fully realized, concerted efforts in technical standardization, robust biomarker qualification, and the development of shared computational frameworks are urgently needed.

Keywords: Quantitative Imaging Biomarkers; Pharmacokinetic-Pharmacodynamic Modeling; Clinical Trials; Surrogate Endpoints; Translational Medicine

Introduction

The contemporary landscape of drug development, particularly in complex fields like oncology and neurodegenerative diseases, is characterized by staggering costs, prolonged timelines, and daunting failure rates, especially in Phase II and III clinical trials (DiMasi et al., 2016). A primary contributor to these failures is the frequent reliance on empirical dosing and late-stage clinical endpoints (like overall survival), which provide limited mechanistic insight early in development. Traditional pharmacokinetic/pharmacodynamic (PK/PD) modeling has long served as a cornerstone for rational drug development, mathematically linking

*Corresponding author e-mail: halkhayyal@moh.gov.sa (Hamad Abdulelah H Alkhayyal).

Receive Date: 21 December 2024, Revise Date: 30 December 2024, Accept Date: 31 December 2024

systemic drug exposure (PK) to a measurable biological or clinical effect (PD) (Falkenhagen et al., 2023). However, conventional PD endpoints—such as serum biomarkers or infrequent, invasive tissue biopsies—offer a spatially and temporally limited snapshot, failing to capture the profound inter- and intra-lesional heterogeneity that is a hallmark of diseases like cancer (Wang et al., 2023).

Concurrently, the field of radiology has undergone a quantitative revolution. Modern imaging modalities have evolved from purely descriptive tools into rich sources of *in vivo* data on pathophysiology (Schuhmacher et al., 2023). Techniques like Dynamic Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI), Diffusion-Weighted Imaging (DWI), and molecular imaging with Positron Emission Tomography (PET) generate quantifiable parameters related to tissue vascularity, cellular density, and metabolic activity (O'Connor et al., 2017). These quantitative imaging biomarkers (QIBs)—defined as objectively measured characteristics derived from an image as an indicator of normal biological processes, pathogenic processes, or responses to a therapeutic intervention—are inherently suitable for integration into mathematical models (Sullivan et al., 2015).

The convergence of advanced PK/PD modeling and quantitative imaging represents a powerful and necessary evolution in translational medicine. This paradigm, often termed imaging PK/PD or pharmaco-imaging, seeks to use non-invasive imaging data to inform and populate computational models of drug action *in vivo* (Sander & Hesse, 2017; O'Connor et al., 2017). By doing so, it addresses critical questions in early-phase trials: Is the drug reaching its intended target at sufficient concentrations? Is it engaging the target (e.g., receptor occupancy)? Is there an early, measurable biological effect that predicts eventual clinical benefit? This narrative review synthesizes the current methodologies for deriving PK/PD parameters from imaging data, explores their application across key therapeutic areas, and critically examines the challenges and future directions for establishing imaging biomarkers as qualified surrogate endpoints in clinical trials.

Key Quantitative Imaging Modalities and Their PK/PD-Relevant Parameters

To understand imaging-informed PK/PD, one must first appreciate the biophysical basis of the primary QIBs and the models used to extract them. These modalities move beyond structural size measurements (e.g., RECIST 1.1) to probe function and microenvironment (Table 1).

Dynamic Contrast-Enhanced MRI (DCE-MRI)

DCE-MRI involves the rapid serial acquisition of T1-weighted images before, during, and after the intravenous administration of a gadolinium-based contrast agent. By analyzing the signal intensity time course within a tissue of interest (e.g., a tumor), one can apply tracer kinetic models, such as the Tofts model, to estimate parameters like K*trans* (volume transfer constant), which reflects blood flow and vascular permeability, and **v*e*** (extravascular extracellular volume fraction) (Zhao et al., 2017). In a PK/PD context, a decrease in K*trans* following treatment with an anti-angiogenic agent provides a direct, localized PD measure of the drug's effect on tumor vasculature. Furthermore, the contrast agent's kinetics can be modeled analogously to a drug, providing insights into tissue perfusion and vascular integrity—key determinants of drug delivery (O'Connor et al., 2011).

Diffusion-Weighted Imaging (DWI) and Apparent Diffusion Coefficient (ADC)

DWI measures the random Brownian motion of water molecules in tissue. In highly cellular tissues like tumors, water diffusion is restricted. The Apparent Diffusion Coefficient (ADC), derived from DWI, is a quantitative measure of this diffusivity (Koh & Collins, 2007). An increase in ADC following effective cytotoxic or targeted therapy often precedes tumor shrinkage, reflecting cell death, loss of membrane integrity, and a reduction in cellular density. This makes ADC a sensitive early PD biomarker of treatment-induced cellular response, valuable for assessing drug efficacy weeks before morphological changes are apparent (Thoeny et al., 2012).

Positron Emission Tomography (PET)

PET is the quintessential molecular imaging modality for PK/PD. By using radiolabeled tracers, it can quantify specific biological processes. Tracer PK/PD is a direct application: a radiolabeled version of the drug itself (e.g., [^{11}C]erlotinib) can be used to directly visualize and quantify its tissue distribution, binding, and clearance—essentially providing a non-invasive PK map (Saleem et al., 2001; Dunphy & Pillarsetty, 2020). Alternatively, PD tracers can be used: a reduction in [^{18}F]FDG (fluorodeoxyglucose) SUV (Standardized Uptake Value) indicates decreased glucose metabolism, a common response to effective therapy. More specific tracers can target receptors (e.g., [^{68}Ga]DOTATATE for somatostatin receptors), allowing for the assessment of target expression (patient stratification) and occupancy after drug administration (a direct PD endpoint) (Lopci et al., 2014). Figure 1 illustrates the integration of quantitative imaging biomarkers (QIBs) into pharmacokinetic/pharmacodynamic (PK/PD) modeling.

Table 1: Key Quantitative Imaging Modalities and Their PK/PD-Relevant Parameters

Imaging Modality	Primary Biomarker(s)	Biological/Physiological Meaning	PK/PD Role & Example Drug Class

Dynamic Contrast-Enhanced MRI (DCE-MRI)	K*trans* (transfer constant), v*e* (extravascular volume), k*ep* (reflux rate)	Tissue perfusion, capillary permeability, extracellular space.	**PD Biomarker:** Measures anti-angiogenic effect. E.g., Decrease in K*trans* after VEGF inhibitor therapy. Can inform on drug delivery.
Diffusion-Weighted MRI (DW-MRI)	Apparent Diffusion Coefficient (ADC)	Water molecule diffusivity, inversely related to tissue cellularity.	**Early PD Biomarker:** Increase in ADC indicates cell death/lysis. E.g., Response to cytotoxic chemo or targeted therapy.
PET with [^{18}F]FDG	Standardized Uptake Value (SUV), Metabolic Tumor Volume (MTV)	Glucose metabolism, a surrogate for cellular proliferation and viability.	**PD Biomarker:** Decrease in SUV indicates metabolic response. Used across many oncology trials.
PET with Drug-Analogue Tracer	Tissue SUV, Volume of Distribution (V*T*)	Direct distribution and binding of the drug molecule itself.	**Direct PK Biomarker:** Maps tissue concentration-time profile. E.g., [^{11}C]erlotinib for lung cancer.
PET with Target-Specific Tracer	Receptor Binding Potential (BP*ND*), SUV	Target/receptor density and occupancy.	**Stratification & PD Biomarker:** Assesses target expression pre-dose and receptor occupancy post-dose. E.g., [^{68}Ga]DOTATATE & somatostatin receptor inhibitors.

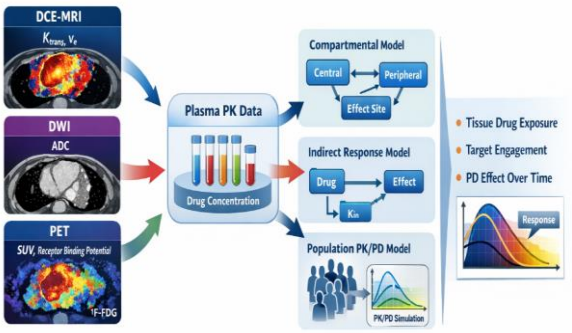

Figure 1. Multimodal Quantitative Imaging Biomarkers Integrated into PK/PD Modeling

Integrating Imaging Data into PK/PD Modeling Frameworks

The true power of QIBs is unlocked when they are quantitatively integrated into mathematical PK/PD models. This integration moves beyond simple correlation to a mechanistic understanding (Table 2).

From Image-Derived Curve to PK Parameter

The most direct integration is in compartmental PK modeling using PET. Here, the time-activity curve (TAC) from a dynamic PET scan, representing tracer concentration in tissue, is analyzed using models identical to those used for plasma PK. For a receptor-binding drug analogue, a two-tissue compartment model can estimate the volume of distribution (V*T*) and binding potential (BP*ND*), which relate directly to receptor density and affinity (Innis et al., 2007). This allows for the non-invasive estimation of traditional PK parameters at the site of action, a monumental leap over plasma sampling alone.

Linking Systemic PK to Local PD via Imaging

A common modeling framework is the indirect response model, where the drug's plasma PK (driving force) is linked to an imaging PD endpoint via an effect compartment. For example, a model can describe how the plasma concentration of an anti-angiogenic drug inhibits the "production" of K*trans* (representing vascular permeability), leading to a gradual decrease in the DCE-MRI parameter (Choi et al., 2016). These models can characterize the delay (hysteresis) between plasma exposure and tissue effect and can be used to simulate different dosing regimens to optimize the PD response.

Population PK/PD Modeling with Imaging Endpoints

Imaging data, often longitudinal and collected from multiple patients, is ideally suited for **nonlinear** mixed-effects modeling (NONMEM). Population PK/PD models can be developed where the typical time course of an imaging biomarker (e.g., ADC change) is described, and inter-individual variability is quantified and related to patient covariates (e.g., genotype, renal function) (Mould & Upton, 2013). This approach is powerful for identifying subpopulations with distinct PK/PD profiles and for optimizing trial design through simulation.

Spatially-Resolved and Multiscale Modeling

A frontier in the field is moving beyond "whole-tumor" average values. By applying PK/PD models on a voxel-by-voxel basis, researchers can create parametric maps of drug effect, revealing intratumoral heterogeneity in drug delivery and response. Furthermore, multiscale models attempt to link imaging biomarkers (tissue-scale) with underlying cellular and molecular processes, providing a more integrated systems pharmacology view (Hormuth et al., 2021). Figure 2 depicts voxel-based and spatial PK/PD modeling using quantitative

imaging. Parametric maps derived from longitudinal DCE-MRI, DWI, and PET visualize intratumoral heterogeneity in perfusion, cellularity, and metabolism before and after therapy.

Table 2: Common PK/PD Modeling Frameworks Integrating Quantitative Imaging Biomarkers

Modeling Framework	Primary Imaging Input	Model Output/Purpose	Key Advantage	Example Application
Compartmental PK Model (PET)	Time-Activity Curve (TAC) from dynamic PET scan.	Volume of Distribution (V*T*), Binding Potential (BP), receptor occupancy.	Provides non-invasive, tissue-specific PK parameters and direct target engagement data.	Estimating brain penetration and dopamine D2 receptor occupancy of an antipsychotic using [^{11}C]raclopride PET.
Indirect Response (IDR) Model	Longitudinal measurements of a QIB (e.g., K*trans*, ADC, SUV).	Estimates of drug potency (EC*50*), signal transduction delay, maximal effect (E*max*).	Mechanistically links plasma PK to the time course of a biological effect measured by imaging.	Modeling the slow decrease in tumor K*trans* after a single dose of a VEGF inhibitor, linking plasma levels to anti-angiogenic effect.
Population PK/PD Model (Nonlinear Mixed-Effects)	Sparse, longitudinal imaging data from a cohort of patients.	Population typical values, variability, and covariate effects (e.g., weight, genotype on PD).	Efficiently handles sparse, real-world trial data; identifies sources of variability; enables trial simulation.	Characterizing the population relationship between antibody dose, serum levels, and change in [^{18}F]FDG SUV in lymphoma patients.
Voxel-Based or Spatial PK/PD Model	Full imaging dataset (e.g., all voxels in a tumor).	Parametric maps of drug effect (e.g., local K*trans* change), revealing heterogeneity.	Moves beyond whole-lesion averages to analyze spatial patterns of response and resistance.	Mapping regions of persistent high cellularity (low ADC) within a responding tumor to guide biopsy or radiotherapy.

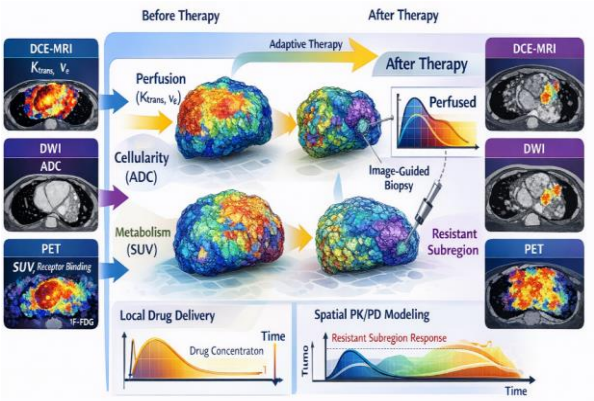

Figure 2. Spatially Resolved Imaging PK/PD for Assessing Tumor Heterogeneity and Treatment Response

Applications in Clinical Trial Design and Decision-Making

The integration of imaging PK/PD is reshaping the conduct and analysis of clinical trials, particularly in early (Phase I/II) stages.

Phase 0/Microdosing Trials with Imaging

These exploratory first-in-human trials administer sub-therapeutic doses of a radiolabeled drug to primarily assess its tissue distribution and PK using PET (Cho et al., 2023). This approach, sanctioned by regulatory agencies like the FDA's Exploratory IND guidance, provides critical human PK data early, de-risking later development by confirming the drug reaches its target organ (e.g., brain penetration for a neurotherapeutic) (Burt et al., 2016).

Determining Biologically Effective Dose (BED)

Traditional Phase I trials aim to find the Maximum Tolerated Dose (MTD). Imaging PK/PD enables a more nuanced objective: finding the Biologically Effective Dose (BED). By modeling the relationship between drug exposure and a relevant imaging PD endpoint (e.g., receptor occupancy on PET, change in ADC), investigators can identify the dose that saturates the target or produces a near-maximal biological effect, which may be lower and safer than the MTD (Yap et al., 2015; Nass et al., 2018). This is a paradigm shift towards mechanism-driven dosing.

Go/No-Go Decisions and Patient Stratification

Imaging biomarkers are increasingly used as primary or key secondary endpoints in proof-of-concept Phase II trials. A significant change in an imaging biomarker (e.g., metabolic response on FDG-PET per PERCIST criteria) can provide early evidence of biological activity, informing go/no-go decisions for costly Phase III trials (Miceli et al., 2023). Furthermore, baseline imaging can stratify patients: only those with tumors expressing the target (e.g., high somatostatin receptor uptake on PET) are enrolled in a trial for a corresponding targeted therapy, enriching

the population for potential responders (de Herder et al., 2003).

Therapeutic Area Spotlight – Oncology

Oncology is the most advanced field for imaging PK/PD. Applications include: monitoring the vascular normalization window with DCE-MRI after anti-angiogenics to optimize combination therapy timing; using early ADC increase to predict long-term response to neoadjuvant chemotherapy; and using FLT-PET (a proliferation marker) to assess the cytostatic effect of targeted agents (O'Connor et al., 2017; Thoeny et al., 2012).

Therapeutic Area Spotlight - Neurology & Psychiatry

In CNS drug development, a major hurdle is the blood-brain barrier (BBB). PET imaging with a drug analogue is the definitive method to confirm brain penetration and measure target occupancy (e.g., amyloid plaque occupancy with [^{11}C]PIB, dopamine receptor occupancy). This data is now routinely used to select clinical doses for trials in Alzheimer's disease, schizophrenia, and depression (Nerella et al., 2022).

Challenges, Validation, and the Path to Regulatory Qualification

Despite its promise, the widespread adoption of imaging biomarkers in regulatory decision-making faces significant hurdles.

A QIB must be accurate, precise, and repeatable. Variations in scanner hardware, acquisition protocols, and analysis software can introduce unacceptable variability. Initiatives like the Quantitative Imaging Biomarkers Alliance (QIBA) from the RSNA are developing standardized profiles (e.g., for DCE-MRI, FDG-PET) to ensure consistent measurement across sites in multi-center trials (Sullivan et al., 2015).

There is a crucial distinction between technical validation (is the measurement robust?) and clinical qualification (does the biomarker meaningfully predict clinical outcome?). The path to qualification requires prospective demonstration that a change in the imaging biomarker reliably predicts a later, clinically meaningful endpoint (e.g., progression-free or overall survival) (FDA-NIH Biomarker Working Group, 2022). This is a high bar, requiring large, costly studies. Meta-analyses of historical trial data can support qualification efforts.

While regulatory agencies (FDA, EMA) are increasingly open to imaging endpoints, they require a clear, pre-specified analysis plan and evidence of rigorous standardization. PERCIST is an example of a qualified methodology for FDG-PET in lymphoma and other cancers (Kitajima et al., 2020). However, for most novel QIBs, acceptance is on a case-by-case basis. Engaging with regulators early through avenues like the FDA's Biomarker Qualification Program is essential.

Imaging PK/PD generates large, complex datasets ("radiomics"). Analyzing this data requires sophisticated bioinformatics, robust statistical methods to handle multiple comparisons, and shared computational platforms to ensure reproducibility of complex modeling workflows (Wichtmann et al., 2023).

Advanced imaging and analysis are expensive and add complexity to trial conduct. A compelling value proposition must be demonstrated—that the upfront cost and complexity are offset by a higher probability of trial success, earlier termination of ineffective drugs, and more efficient dose selection.

Conclusion and Future Directions

The integration of quantitative imaging biomarkers into pharmacokinetic/pharmacodynamic modeling represents a paradigm shift in clinical pharmacology and translational drug development. It transforms medical imaging from a diagnostic tool into a dynamic, *in vivo* assay system, providing a non-invasive window into drug distribution, target engagement, and early therapeutic response. By populating mechanistic PK/PD models, QIBs enable a more rational, efficient, and informative clinical trial process—from microdosing studies that confirm tissue penetration, to Phase I trials that define a biologically effective dose, to Phase II trials that provide early proof of mechanism.

The future trajectory of this field is poised along several exciting axes. First, the rise of radiomics and artificial intelligence promises to extract even more sub-visual, high-dimensional data from standard medical images, potentially revealing novel PK/PD relationships and predictive signatures (Gillies et al., 2016). Second, the integration of imaging data with other "omics" layers (genomics, proteomics) in a systems pharmacology framework will enable a more holistic, personalized understanding of drug response and resistance (Chauvie et al., 2023). Third, the application of these principles is expanding beyond oncology and neurology into areas like cardiology, rheumatology, and infectious diseases.

However, for this potential to be fully realized, the community must collectively address the persistent challenges of standardization, validation, and qualification. This requires sustained collaboration among clinical pharmacologists, radiologists, imaging scientists, biostatisticians, regulatory scientists, and industry sponsors. The development of open-source, validated software platforms for imaging PK/PD analysis and the continued growth of consortia like QIBA are critical steps. By solidifying the methodological rigor and evidential basis of imaging biomarkers, we can accelerate the delivery of effective therapies to patients, ensuring that the promising convergence of imaging and modeling truly shortens the path from bench to bedside.

References

1. Burt, T., Yoshida, K., Lappin, G., Vuong, L., John, C., De Wildt, S. N., ... & Rowland, M.

(2016). Microdosing and other phase 0 clinical trials: facilitating translation in drug development. *Clinical and translational science*, *9*(2), 74. https://doi.org/10.1111/cts.12390

2. Chauvie, S., Mazzoni, L. N., & O'Doherty, J. (2023). A review on the use of imaging biomarkers in oncology clinical trials: quality assurance strategies for technical validation. *Tomography*, *9*(5), 1876-1902. https://doi.org/10.3390/tomography9050149
3. Cho, N. S., Wong, W. K., Nghiemphu, P. L., Cloughesy, T. F., & Ellingson, B. M. (2023). The future glioblastoma clinical trials landscape: early phase 0, window of opportunity, and adaptive phase I–III studies. *Current Oncology Reports*, *25*(9), 1047-1055. https://doi.org/10.1007/s11912-023-01433-1
4. Choi, S. H., Jung, S. C., Kim, K. W., Lee, J. Y., Choi, Y., Park, S. H., & Kim, H. S. (2016). Perfusion MRI as the predictive/prognostic and pharmacodynamic biomarkers in recurrent malignant glioma treated with bevacizumab: a systematic review and a time-to-event meta-analysis. *Journal of Neuro-oncology*, *128*(2), 185-194. https://doi.org/10.1007/s11060-016-2102-4
5. De Herder, W. W., Hofland, L. J., van der Lely, A. J., & Lamberts, S. W. J. (2003). Somatostatin receptors in gastroentero-pancreatic neuroendocrine tumours. *Endocrine-related cancer*, *10*(4), 451-458.
6. DiMasi, J. A., Grabowski, H. G., & Hansen, R. W. (2016). Innovation in the pharmaceutical industry: new estimates of R&D costs. *Journal of health economics*, *47*, 20-33. https://doi.org/10.1016/j.jhealeco.2016.01.012
7. Dunphy, M. P., & Pillarsetty, N. (2020). The unique pharmacometrics of small molecule therapeutic drug tracer imaging for clinical oncology. *Cancers*, *12*(9), 2712. https://doi.org/10.3390/cancers12092712
8. Falkenhagen, U., Knöchel, J., Kloft, C., & Huisinga, W. (2023). Deriving mechanism-based pharmacodynamic models by reducing quantitative systems pharmacology models: An application to warfarin. *CPT: pharmacometrics & systems pharmacology*, *12*(4), 432-443. https://doi.org/10.1002/psp4.12903
9. FDA-NIH Biomarker Working Group. (2022). *BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2016 [cited 2020]*.
10. Gillies, R. J., Kinahan, P. E., & Hricak, H. (2016). Radiomics: images are more than pictures, they are data. *Radiology*, *278*(2), 563-577. https://doi.org/10.1148/radiol.2015151169
11. Hormuth, D. A., Phillips, C. M., Wu, C., Lima, E. A., Lorenzo, G., Jha, P. K., ... & Yankeelov, T. E. (2021). Biologically-based mathematical modeling of tumor vasculature and angiogenesis via time-resolved imaging data. *Cancers*, *13*(12), 3008. https://doi.org/10.3390/cancers13123008
12. Innis, R. B., Cunningham, V. J., Delforge, J., Fujita, M., Gjedde, A., Gunn, R. N., ... & Carson, R. E. (2007). Consensus nomenclature for in vivo imaging of reversibly binding radioligands. *Journal of Cerebral Blood Flow & Metabolism*, *27*(9), 1533-1539. https://doi.org/10.1038/sj.jcbfm.9600493
13. Kitajima, K., Maruyama, M., Minami, T., Yokoi, T., Kuribayashi, K., Kijima, T., ... & Yamakado, K. (2020). Comparison of modified Response Evaluation Criteria in Solid Tumors, European Organization for Research and Treatment of Cancer criteria, and PET Response Criteria in Solid Tumors for evaluation of tumor response to chemotherapy and prognosis prediction in patients with unresectable malignant pleural mesothelioma. *Nuclear Medicine Communications*, *41*(8), 790-799. *DOI:* 10.1097/MNM.0000000000001223
14. Koh, D. M., & Collins, D. J. (2007). Diffusion-weighted MRI in the body: applications and challenges in oncology. *American Journal of Roentgenology*, *188*(6), 1622-1635. https://doi.org/10.2214/AJR.06.1403
15. Lopci, E., Grassi, I., Chiti, A., Nanni, C., Cicoria, G., Toschi, L., ... & Fanti, S. (2014). PET radiopharmaceuticals for imaging of tumor hypoxia: a review of the evidence. *American journal of nuclear medicine and molecular imaging*, *4*(4), 365.
16. Miceli, A., Jonghi-Lavarini, L., Santo, G., Cassarino, G., Linguanti, F., Gazzilli, M., ... & Nappi, A. G. (2023). [18F] FDG PET/CT criteria for treatment response assessment: EORTC and beyond. *Clinical and Translational Imaging*, *11*(5), 421-437. https://doi.org/10.1007/s40336-023-00578-0
17. Mould, D. R., & Upton, R. N. (2013). Basic concepts in population modeling, simulation, and model-based drug development—part 2: introduction to pharmacokinetic modeling methods. *CPT: pharmacometrics & systems pharmacology*, *2*(4), 1-14. https://doi.org/10.1038/psp.2013.14
18. Nass, S. J., Rothenberg, M. L., Pentz, R., Hricak, H., Abernethy, A., Anderson, K., ... & Schilsky, R. L. (2018). Accelerating anticancer drug development—opportunities and trade-offs. *Nature Reviews Clinical Oncology*, *15*(12), 777-786. https://doi.org/10.1038/s41571-018-0102-3
19. Nerella, S. G., Singh, P., Sanam, T., & Digwal, C. S. (2022). PET molecular imaging in drug development: the imaging and chemistry perspective. *Frontiers in medicine*, *9*, 812270. https://doi.org/10.3389/fmed.2022.812270

20. O'Connor, J. P., Jackson, A., Parker, G. J., & Jayson, G. C. (2007). DCE-MRI biomarkers in the clinical evaluation of antiangiogenic and vascular disrupting agents. *British journal of cancer*, *96*(2), 189-195. https://doi.org/10.1038/sj.bjc.6603515
21. O'Connor, J. P., Rose, C. J., Waterton, J. C., Carano, R. A., Parker, G. J., & Jackson, A. (2015). Imaging intratumor heterogeneity: role in therapy response, resistance, and clinical outcome. *Clinical Cancer Research*, *21*(2), 249-257. https://doi.org/10.1158/1078-0432.CCR-14-0990
22. O'connor, J. P. B., Tofts, P. S., Miles, K. A., Parkes, L. M., Thompson, G., & Jackson, A. (2011). Dynamic contrast-enhanced imaging techniques: CT and MRI. *The British journal of radiology*, *84*(special_issue_2), S112-S120. https://doi.org/10.1259/bjr/55166688
23. O'connor, J. P., Aboagye, E. O., Adams, J. E., Aerts, H. J., Barrington, S. F., Beer, A. J., ... & Waterton, J. C. (2017). Imaging biomarker roadmap for cancer studies. *Nature reviews Clinical oncology*, *14*(3), 169-186. https://doi.org/10.1038/nrclinonc.2016.162
24. Saleem, A., Harte, R. J., Matthews, J. C., Osman, S., Brady, F., Luthra, S. K., ... & Aboagye, E. O. (2001). Pharmacokinetic evaluation of N-[2-(dimethylamino) ethyl] acridine-4-carboxamide in patients by positron emission tomography. *Journal of clinical oncology*, *19*(5), 1421-1429. https://doi.org/10.1200/JCO.2001.19.5.1421
25. Sander, C. Y., & Hesse, S. (2017). News and views on in vivo imaging of neurotransmission using PET and MRI. *The quarterly journal of nuclear medicine and molecular imaging: official publication of the Italian Association of Nuclear Medicine (AIMN)[and] the International Association of Radiopharmacology (IAR),[and] Section of the Society of...*, *61*(4), 414. https://doi.org/10.23736/S1824-4785.17.03019-9
26. Schuhmacher, A., Hinder, M., und Stein, A. V. S., Hartl, D., & Gassmann, O. (2023). Analysis of pharma R&D productivity–a new perspective needed. *Drug Discovery Today*, *28*(10), 103726. https://doi.org/10.1016/j.drudis.2023.103726
27. Sullivan, D. C., Obuchowski, N. A., Kessler, L. G., Raunig, D. L., Gatsonis, C., Huang, E. P., ... & RSNA-QIBA Metrology Working Group. (2015). Metrology standards for quantitative imaging biomarkers. *Radiology*, *277*(3), 813-825. https://doi.org/10.1148/radiol.2015142202
28. Thoeny, H. C., Forstner, R., & De Keyzer, F. (2012). Genitourinary applications of diffusion-weighted MR imaging in the pelvis. *Radiology*, *263*(2), 326-342. https://doi.org/10.1148/radiol.12110446
29. Wang, C., Bai, R., Liu, Y., Wang, K., Wang, Y., Yang, J., ... & Yang, P. (2023). Multi-region sequencing depicts intratumor heterogeneity and clonal evolution in cervical cancer. *Medical Oncology*, *40*(2), 78. https://doi.org/10.1007/s12032-022-01942-2
30. Wichtmann, B. D., Harder, F. N., Weiss, K., Schönberg, S. O., Attenberger, U. I., Alkadhi, H., ... & Baeßler, B. (2023). Influence of image processing on radiomic features from magnetic resonance imaging. *Investigative Radiology*, *58*(3), 199-208. *DOI:* 10.1097/RLI.0000000000000921
31. Yap, T. A., Bjerke, L., Clarke, P. A., & Workman, P. (2015). Drugging PI3K in cancer: refining targets and therapeutic strategies. *Current opinion in pharmacology*, *23*, 98-107. https://doi.org/10.1016/j.coph.2015.05.016
32. Zhao, M., Guo, L. L., Huang, N., Wu, Q., Zhou, L., Zhao, H., ... & Fu, K. (2017). Quantitative analysis of permeability for glioma grading using dynamic contrast-enhanced magnetic resonance imaging. *Oncology letters*, *14*(5), 5418-5426. https://doi.org/10.3892/ol.2017.6895

.